167

(b)(3)

THE ADDICTION LIABILITIES OF SYNTHETIC SUBSTITUTES FOR CODEINE

Harris Isbell
NIMH Addiction Research Center, Lexington, Ky.

H. F. Fraser and A. Wikler

101-149 NAonr-14-60

To develop adequate synthetic substitutes for codeine, the opiate which is most widely used in medical practice, and for which there is no domestic natural source of supply.

The most satisfactory analgesic substitutes for codeine so far developed are d-propoxyphene (Darvon, Lilly) and ethoheptazine (Zactirin, Wyeth). They are substantially less addicting than codeine and neither is subject to narcotic control but they are not as effective as codeine in relief of pain. Two effective cough suppressants have been discovered and are on the market. They are dextromethorphan, Romilar, a synthetic, and narcotine a by-product of opium processing. A potent synthetic anti-diarrheal or constipating agent (R-1132) has also been discovered which is effective in doses of 5-10 mg three times daily. It has definite addiction liability but most probably it would be less subject to abuse than codeine.

During the current year advances were made in the methodology for measuring abuse-liability of new drugs. By employing a specially devised "attitude" questionnaire, it was found that there is considerable variation among narcotic drugs insofar as they are identified as "dope" (opiates), and addicts express definite preferences. As an adjunct to objective measurements such an "attitude" questionnaire should be useful and simple procedure for evaluating the relative abuse liability of new synthetics. Formerly in man, the method for evaluating drugs by direct addiction (a procedure which simulates that employed by the addict in his abuse of drugs) required from two to six months to complete. Experiments during the current year demonstrated that in the cases of morphine, codeine and heroin, a relatively high degree of tolerance and physical dependence develope when these drugs are chronically administered for only 18-20 days. This shortened "abuse" procedure has made it possible to compare the addiction liabilities of several new synthetic opiate-like drugs

B-294

with that of morphine in the same individuals.

Addiction studies were completed on 9 new compounds. Evaluation of two of these has been submitted to the Committee on Drug Addiction and Narcotics, National Research Council (phenazocine and levophenacylmorphan). Both of these drugs were more potent than morphine in inducing morphine-like "euphoria" and behavior and both completely substituted for morphine in addicted persons. Although definite physical dependence developed following chronic administration of both of these compounds, the degree of physical dependence was less than that observed in the case of morphine. Their effectiveness by the oral route has been inadequately explored.

A compound related to nalorphine structurally (l-3-hydroxy-N-gamma gamma-dimethylallylmorphinan) was tested for addiction liability. In postaddicts, its effects resemble those of morphine, rather than nalorphine and therefore it has no advantages as a substitute for codeine.

A new very potent compound, 1-(Beta-diethylaminoethyl)-2-(p-ethoxy-benzyl)-5-nitrobenzimidazole methane sulfonate, has been developed by Ciba. In man, the euphoriant dose, on oral administration, was about 0.25 mg (80-120 times as potent as oral morphine). It was 60 times as effective orally as morphine is subcutaneously in suppressing abstinence from morphine. During chronic administration, postaddicts were much impressed by its overall sedative effects, although they recognized it as opiate-like. Since the compound induces definite tolerance and physical dependence its addiction liability would approximate that of morphine.

PLANS FOR FUTURE

Studies on several compounds have been completed and these will be prepared for publication. New drugs to be studied are (a) a butyl ester of R-1132 (the antidiarrheal agent), (b) the methyl analogue of phenazocine (the counterpart of codeine in this series) and (c) l-3-hydroxy-N-propargyl-morphinan hydrobromide, an analgesic which is a morphine antagonist, and hence probably of low addiction liability. From the long-range point of view it is intended to continue the search for substitutes for codeine until drugs are found which are, in the opinion of the Committee on Drug Addiction and Narcotics, completely satisfactory substitutes for codeine.

CURRENT REPORTS AND PUBLICATIONS

(a) H. F. Fraser and Harris Isbell (1959), "Addiction liabilities of (a) dl-2'-Hydroxy-5,9-dimethyl-2 (phenethyl)-6,7-benzmorphan HBr (NIH-7519), and (b) l-3-Hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525)." Addendum 3, Min. 20th Meet., Committee on Drug Addiction and Narcotics, Nat. Res. Council. Washington, D.C. Natl. Acad. Sci.

(6)(3)

THE ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE

(Project Description)

Request to the Office of Naval Research for Renewal of

Task No. NR 101-149
Contract NAonr-144-60

1. Background Information.

Since 1951 the National Institute of Mental Health Addiction Research Center, U. S. Public Health Service Hospital, Lexington, Ky., has been carrying on a project designed to develop a synthetic substitute for codeine which would be as safe as codeine and as effective with respect to toxicity, antitussive activity, constipative activity, and addiction liability. The project has been financed in large part by funds from the Office of Naval Research, and this description constitutes a request for renewal of the project for the period 1 July 1960 to 30 June 1961.

The project was initiated because synthetic substitutes for codeine were badly needed since opium or morphine derived from opium constitute the only sources of codeine. Codeine is the most widely used narcotic drug in both civilian and military medical practice. The United States consumes 16 to 20 tons of this drug yearly so that, unless adequate synthetic substitutes are found, the nation must continue to stockpile opium or morphine

B-292

in order to provide adequate supplies for both the civilian and military population in the event of war. The facilities of the NIMH Addiction Research Center are not sufficient to carry out this work in addition to the evaluation of potent new analgesics submitted by the Committee on Drug Addiction and Narcotics, National Research Council, unless additional funds are supplied through the Department of Defense.

2. Work Accomplished to Date.

The most satisfactory analgesic substitutes for codeine so far developed are d-propoxyphene (Darvon, Lilly) and ethoheptazine (Zactirin, Wyeth). They are substantially less addicting than codeine and neither is subject to narcotic control but they are not as effective as codeine in relief of pain. Two effective cough suppressants have been discovered and are on the market. They are dextromethorphan, Romilar, a synthetic, and narcotine, a by-product of opium processing. A potent synthetic antidiarrheal or constipating agent (R-1132) has also been discovered which is effective in doses of 5-10 mg three times daily. It has definite addiction liability but most probably it would be less subject to abuse than codeine.

During the current year advances were made in the methodology for measuring abuse-liability of new drugs. By employing a specially devised "attitude" questionnaire, it

was found that there is considerable variation among narcotic drugs insofar as they are identified as "dope" (opiates), and addicts express definite preferences. As an adjunct to objective measurements such an "attitude" questionnaire should be useful and simple procedure for evaluating the relative abuse liability of new synthetics. Formerly in man, the method for evaluating drugs by direct addiction (a procedure which simulates that employed by the addict in his abuse of drugs) required from two to six months to complete. Experiments during the current year demonstrated that in the cases of morphine, codeine and heroin, a relatively high degree of tolerance and physical dependence develops when these drugs are chronically administered for only 18-20 days. This shortened "abuse" procedure has made it possible to compare the addiction liabilities of several new synthetic opiate-like drugs with that of morphine in the same individuals.

Addiction studies were completed on 9 new compounds. Evaluation of two of these has been submitted to the Committee on Drug Addiction and Narcotics, National Research Council (phenazocine and levophenacylmorphan). Both of these drugs were more potent than morphine in inducing morphine-like "euphoria" and behavior and both completely substituted for morphine in addicted persons. Although definite physical

dependence developed following chronic administration of both of these compounds, the degree of physical dependence was less than that observed in the case of morphine. Their effectiveness by the oral route has been inadequately explored.

A compound related to nalorphine structurally (1-3-hydroxy-N-gamma gamma-dimethylallylmorphinan) was tested for addiction liability. In postaddicts, its effects resemble those of morphine, rather than nalorphine and therefore it has no advantages as a substitute for codeine.

A new very potent compound, 1-(Beta-diethylaminoethyl)-2-(p-ethoxy-benzyl)-5-nitrobenzimidazole methane sulfonate, has been developed by Ciba. In man, the euphoriant dose, on oral administration, was about 0.25 mg (80-120 times as potent as oral morphine). It was 60 times as effective orally as morphine is subcutaneously in suppressing abstinence from morphine. During chronic administration, postaddicts were much impressed by its overall sedative effects, although they recognized it as opiate-like. Since the compound induces definite tolerance and physical dependence its addiction liability would approximate that of morphine

3. Need for Continuation of the Project.

At present, the chief justification for continuation of the project is the urgent need for a substitute for relief of mild

grades of pain. As pointed out above, propoxyphene no longer seems to be as promising as was originally hoped. At the moment no completely satisfactory substitute for codeine for pain relief has been found. For this reason it is essential to continue the search.

4. Work Proposed.

During the period from 1 July 1960 to 30 June 1961 we propose to test the clinical pharmacology and addictive properties of a butyl ester of R-1132 (1-(3-diphenyl-3-carbonitril-propyl)-4-phenyl-4-carbethoxypiperidine); the methyl analogue of phenazocine (the counterpart of codeine in this series), and l-3-hydroxy-N-propargyl-morphinan hydrobromide, an analgesic which is a morphine-antagonist, and therefore probably of low addiction liability. In addition, studies of other substances regarded as potential codeine substitutes by the Committee on Drug Addiction and Narcotics will be carried out, as advised by that body.

5. Methods.

The methods used are the standard addiction liability testing methods of the NIMH Addiction Research Center. These tests are accepted as legal standards by the Committee on Drug Addiction and Narcotics and have been described in previous project descriptions, which should be consulted for details.

6. Evaluation of Data.

Evaluation of data has been covered in previous project descriptions.

7. Location of the Project.

Work will be carried out in the NIMH Addiction Research Center, PHS Hospital, Lexington, Ky. This institution provides the two necessary facilities for the type of work to be undertaken: (1) pool of patients who will volunteer for experiments with drugs, and (2) strict environmental control, which prevents introduction of drugs other than those under study into the experimental situation.

8. Experimental Personnel.

Work will be carried out under the direction of Harris Isbell, M.D., Director, NIMH Addiction Research Center. This investigator has had fifteen years of experience in research on narcotic drug addiction and has an extensive bibliography in the field. He will be assisted by two other experienced physicians, Dr. H. F. Fraser and Dr. Abraham Wikler, both of whom have had extensive research in this type of work, and many publications. The part-time services of a biochemist, neuropharmacologist, and research psychologist are also available. A special ward for the conduct of these studies has been made available by the hospital and is currently in operation.

9. Estimated Cost.

The estimated costs are shown on the attached sheet. The amount of money requested is only slightly higher than that granted for fiscal year 1960, the difference representing the salary increments of within-grade promotions of the same number of personnel.

Abraham Wikler, M.D.
Acting Director

Attachment
12 November 1959

B-286

Attachment

1. Personal Services:

   4 Medical Aides (GS-6, [redacted])

   1 Psychologist (GS-5)

   1 Clerk-stenographer (GS-4)

   1 Animal Caretaker (GS-3)

   Premium Pay (night differential, holiday pay, etc.) estimate

   Retirement and Insurance*

2. Travel

3. Miscellaneous (supplies, equipment, etc.)

   Total

[redacted]

* This figure does not include cost of Health Insurance, to become effective 1 July 1960, since cost not presently known.

10 November 1959

B-285

#168

THIS DOCUMENT IS BEING WITHHELD IN ITS ENTIRETY.